Association of Serum Vitamin D Levels with Inflammatory Markers in Hospitalized COVID-19 Patients

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Abstract

Background: In recent years, global concern has focused on Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Multiple studies have suggested a potential connection between 1,25-dihydroxy Vitamin D levels and patient prognosis. Inflammatory markers have been identified as useful indicators for assessing the prognosis of hospitalized patients. This study aimed to evaluate the relationship between Vitamin D levels, inflammatory markers, and patient prognosis in cases of COVID-19. Methods: This descriptive-analytical study included 906 patients with COVID-19. Serum Vitamin D levels were measured and categorized into three groups: less than 20 ng/mL, between 20–30 ng/mL, and more than 30 ng/mL. Additionally, inflammatory markers, such as C-reactive protein (CRP) and Lactate Dehydrogenase (LDH), were evaluated. The study also addressed the analysis of CT scan findings and patient prognosis. Results: Of the total patients, 497 (54.9%) were male and 409 were female. The mean serum Vitamin D level was 40.10 ± 37.06 ng/mL, while the mean LDH and mean WBC levels were recorded at 696.38 ± 610.19 U/L and 9058.46 ± 6309.80 per microliter, respectively. CRP levels were classified as +1 in 296 patients (32.7%), +2 in 260 patients (28.7%), and +3 in 7 patients (0.8%). In terms of patient prognosis, 62 patients (6.8%) required intubation, and the mortality rate was 18.0% (163 patients). A statistically significant relationship was found between serum Vitamin D and LDH levels (p = 0.015). The findings indicated an insignificant relationship of serum Vitamin D levels with lymphocyte levels (p = 0.619), body mass index (BMI; p = 0.225), and CRP levels (p = 0.985). Furthermore, no relationship was found between patient mortality and serum Vitamin D levels (p = 0.5). Conclusion: Although Vitamin D has confirmed immunomodulatory effects in many studies, this study found no significant relationship between serum Vitamin D levels and mortality or other inflammatory markers in hospitalized COVID-19 patients. However, a statistically significant correlation was observed between LDH levels and serum Vitamin D.

Keywords: Vitamin D, COVID-19, inflammatory markers, serum LDH, immune response.

Significance | This study determined no significant link between serum Vitamin D levels and COVID-19 mortality, except with LDH.

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Introduction

Vitamin D, an essential organic compound, holds significant importance in enhancing the human immune system. The antibacterial, antiviral, and anti-inflammatory properties of Vitamin D can enhance innate immunity, and regulate adaptive immunity (Hewison, 2011; L. Bishop et al., 2021). Insufficient levels of Vitamin D heighten the susceptibility and severity of viral

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infections (Beard et al., 2011; Spector, 2011). Additionally, a deficiency in Vitamin D heightens the vulnerability to tuberculosis, a condition historically managed with the administration of Vitamin D (Nnoaham & Clarke, 2008; Vinh Quoc Luong & Nguyen, 2011).

In children and adolescents aged 1 to 16 years, dietary supplementation of low doses of Vitamin D may slightly reduce the overall risk of acute respiratory infections, while doses exceeding 1000 international units per day fail to provide such benefits (SACN, 2020). Supplementation significantly reduces moderate to severe exacerbations of chronic obstructive pulmonary disease in individuals with baseline levels of 25(OH)D lower than 25 nanomoles per liter, but not in those with less severe deficiencies (Jolliffe et al., 2019).

Several systematic reviews and meta-analyses have explored the relationship between Vitamin D deficiency and negative outcomes in COVID-19 (Kazemi et al., 2021; Petrelli et al., 2021; Bassatne et al., 2021; Damascena et al., 2021; Dissanayake et al., 2021). Among these, the most extensive analysis scrutinized data from 76 observational studies, including approximately two million adults. The analysis indicated a significant increase in the risk of COVID-19 infection and severe COVID-19 among individuals with Vitamin D deficiency or insufficiency. The odds ratios for these risks were found to be 1.5 and 1.9, respectively. However, it is important to note that these findings were affected by a high risk of bias and heterogeneity. Additionally, this analysis indicated a high rate of mortality although with less certainty (Dissanayake et al., 2021). These findings support earlier, smaller analyses (Kazemi et al., 2021; Petrelli et al., 2021; Bassatne et al., 2021; Damascena et al., 2021), one of which found that COVID-19 patients typically had lower levels of 25(OH)D compared to healthy individuals. Nonetheless, the studies encountered various limitations, including the possibility of reverse causality, which complicated the process of determining the relationship between the studied factors and health outcomes (Bassatne et al., 2021).

According to the US National Institutes of Health (NIH), there is insufficient evidence to determine whether Vitamin D supplements can effectively prevent or treat COVID-19 (Sîrbe et al., 2022). The National Institutes of Health and Nursing (NICE) also do not endorse the use of Vitamin D supplementation as a standalone measure for preventing or treating COVID-19 (Shah et al., 2022; Sobczak & Pawliczak, 2024). The objective of this study was to assess the correlation between serum Vitamin D levels, inflammatory markers, and patient prognosis among hospitalized individuals with COVID-19.

Methodology

This descriptive-analytical study evaluated COVID-19 patients who were hospitalized at Shiraz University of Medical Sciences, Iran, in 2021. The ethics committee of Shiraz University of Medical Sciences confirmed this study and an informed consent was obtained from each patient. The study involved 906 patients who were confirmed positive for SARS-CoV-2 through either a polymerase chain reaction (PCR) analysis or a chest X-ray. Upon admission, the researchers recorded laboratory findings, imaging results (chest X-ray and computed tomography), and clinical data. They also conducted laboratory tests for hospitalized patients, including Vitamin D3, Lactate Dehydrogenase (LDH), lymphocyte count, WBC, and C-reactive protein (CRP). Of note, LDH and CRP were considered inflammatory markers.

The patients were categorized into five groups depending on the type of oxygen therapy they received (reservoir bag, non-invasive ventilation [NIV], intubation, mask, and canal). To compare the data, the researchers categorized serum Vitamin D and LDH levels into different groups. Serum Vitamin D levels were classified as deficient (less than 20 ng/mL), insufficient (between 20 to 30 ng/mL), and sufficient (more than 30 ng/mL) (Dissanayake et al, 2021). Similarly, serum LDH levels were divided into three categories, namely less than 500 U/L, between 500 to 1000 U/L, and more than 1000 U/L (Kazemi et al. 2021).

For the statistical analysis, SPSS software version 26.0 (SPSS, Chicago, Illinois, USA) was used. Continuous data were reported as mean ± standard deviation, while nominal qualitative data were presented as numbers and percentages. The Kruskal-Wallis test was used to explain the differences between the non-parametric continuous distributed variables. The categorical variables were compared using the chi-squared test. The relationship between inflammatory markers and Vitamin D levels was assessed using Spearman's rank correlation test. A p-value of ≤ 0.05 was considered statistically significant.

Results

A total of 906 patients were included in this study, with 497 of them being male (54.9%) and 409 being female. The average age of the patients was 64 ± 16 years. Among them, 399 patients tested positive for PCR, while the remaining (n = 507) tested negative or were admitted to the hospital based on clinical signs. In terms of prognosis, 62 patients (6.9%) required intubation and the mortality rate was 18.4% (167 patients). As can be seen in Table 1, the most prevalent underlying conditions among the patients were Cerebrovascular accident (CVA, 3.8%) and chronic heart failure (CHF, 2.4%). The CRP levels were classified as +1 in 297 patients (32.8%), 2+ in 260 patients (28.7%), and +3 in 7 patients (0.8%). Lymphocyte levels were below 10% in 285 patients and above 10% in 615 patients.

The mean serum Vitamin D level was 40.10 ± 37.06 ng/mL. Mean LDH and WBC levels were 696.38 ± 610.19 U/L and 9058.46 ± 6309.80 per microliter, respectively. The mean body mass index

Table 1. The frequency and percentage of characteristic variables in 906 patients with COVID-19

Variable		Frequency	Percentage
Gender	Male	497	54.9
	Female	409	45.1
Oxygen therapy	Reservoir bag	702	77.5
	Non-invasive ventilation (NIV)	122	13.5
	Intubation	62	6.9
	Mask	13	1.4
	Canal	7	.8
Fate	Alive	739	81.6
	Death	167	18.4
BMI (kg/m^2)	Less than 20	30	3.5
	20 ≤ and < 30	580	67.2
	30 ≤ and < 40	229	26.5
	More than 40	24	2.8
Underlying disease	None	725	80.0
	CVA	34	3.8
	CHF	22	2.4
	Heart disease	20	2.2
	COPD	5	.6
	Kidney disease	1	.1
	Other	99	10.9
CRP	-	284	31.3
	1	297	32.8
	2	260	28.7
	3	7	.8
	None	58	6.4
PCR	Positive	399	44.0
	Negative	353	39.0
	None	154	17.0
Vitamin D (ng/mL)	Less than 20	5	1.2
	20 ≤ and < 30	93	21.5
	More than 30	335	77.4
LDH (U/L)	Less than 500	180	31.1
	500 ≤ and < 1000	344	59.5
	More than 1000	54	9.3
Lymphocyte	More than 10 %	615	68.3
	Less than 10 %	285	31.7

Table 2. The descriptive statistics of Vitamin D Levels and inflammatory markers in 906 patients with COVID-19

		Vitamin3	LDH	Lymphocyte	WBC	BMI	age
N	Valid	433	578	900	894	863	900
	Missing	473	328	6	12	43	6
Mean		40.10	696.38	17.17	9058.46	28.09	64
Standard Deviation		37.06	610.195	11.42	6309.80	5.32	16
Variance		1373.63	372337.45	130.60	39813693.91	28.317	…
Minimum		4.0	151	0	100	.00	…
Maximum		551.0	8900	116	107000	58.59	…

(BMI) was 28.09 ± 5.32 kg/m² (Table 2). In terms of serum Vitamin D levels, 77.4% of patients had levels above 30 ng/mL, 21.5% had levels between 20 and 30 ng/mL, and only 1.2% had levels below 20 ng/mL. As for serum LDH levels, 54 patients had levels above 1000 U/L, 344 had levels between 500 and 1000 U/L, and 180 had levels below 500 U/L.

Approximately 32% of the patients had lymphopenia indicating a lymphocyte percentage below 10. Notably, there was an insignificant statistical relationship between Vitamin D levels and lymphocyte percentage above or below 10 percent ($p = 0.619$). However, there was a statistically significant relationship observed between serum Vitamin D levels and LDH levels ($p = 0.015$). Serum vitamin D levels had no significant statistical relationship with CRP level ($p = 0.985$), lymphocyte level ($p = 0.619$), and BMI ($p = 0.225$). The LDH levels above 1000 U/L did not show a significant association with any serum Vitamin D levels, while LDH levels between 500 and 1000 U/L and less than 500 U/L were significantly associated with serum Vitamin D levels between 20-30 ng/mL and above 30 ng/mL. The study indicated an insignificant statistical relationship between serum Vitamin D levels and type of oxygen therapy ($p = 0.714$) or between serum Vitamin D levels and patient mortality ($p = 0.500$). The obtained results indicated a strong relationship of death among hospitalized COVID-19 patients with intubation ($p < 0.001$), canal ($p < 0.001$), and NIV ($p < 0.001$).

Discussion

In this retrospective study, the goal was to examine the relationship of serum Vitamin D levels with inflammatory markers, in 906 hospitalized patients infected with COVID-19. The obtained results were indicative of no relationship between clinical outcomes of COVID-19 and the initial serum 25-OHD levels, including mortality and levels of inflammatory markers like CRP and lymphocyte count. The only exception was LDH, where a statistically significant association was identified with serum Vitamin D levels. Therefore, it can be concluded that administering Vitamin D supplements does not have a significant impact on outcomes for COVID-19 patients in this study.

Epidemiological evidence has shown a connection between Vitamin D deficiency and increased mortality rates in countries with low levels of 25-OHD (Ilie et al., 2020). Several hospital-based studies have revealed a significant association between low levels of 25-OHD and severe COVID-19 disease (Radujkovic et al., 2020; Maghbooli et al., 2020; Jain et al., 2020). These studies indicated higher levels of inflammatory markers (Jain et al., 2020), ICU admissions (Panagiotou et al., 2020), and mortality (Radujkovic et al., 2020; Baktash et al., 2020). Vitamin D deficiency has been shown to contribute to higher mortality rates among the elderly (Karahan & Katkat, 2020) and a worsened prognosis in individuals with respiratory failure (Carpagnano et al., 2020). However, it is worth noting that most studies have had limited sample sizes.

In the current study, no statistically significant association was found between serum 25-OHD levels and mortality, as well as higher levels of inflammatory markers (except LDH). The mean level of serum Vitamin D in all participants was 40.10 ± 37.06 ng/ml. There was no relationship between serum Vitamin D level and CRP level ($p = 0.985$), or lymphocyte count ($p = 0.619$). However, a statistically significant relationship was observed between serum Vitamin D and LDH levels ($p = 0.015$). Furthermore, serum Vitamin D levels did not correlate with patient mortality ($p = 0.500$). In the same line, Haghighi et al. (2021) also found no relationship between Vitamin D levels and prognostic factors, such as D-dimer, lymphocyte count, and CRP.

In a study conducted in Spain by Hernández et al. (2020), no significant association was found between disease severity and serum 25-OHD levels. However, the study did report significant levels of ferritin in individuals with Vitamin D deficiency, which was left untouched in the current study. In a European study by Pizzini et al. (2020), there was no association between serum 25-OHD levels at the onset of COVID-19 and after 8 weeks, regarding disease severity and lung function impairment.

Conclusion

Although, Vitamin D has immunomodulatory effects that may protect against or alleviate the severity of COVID-19 infection, in this study, no significant connection was found between serum Vitamin D levels and mortality or other inflammatory markers in hospitalized COVID-19 patients. Nevertheless, a statistically significant correlation was observed between serum Vitamin D and LDH levels. Additional research is necessary to investigate the relationship of Vitamin D intake with race and geographical location of patients, as well as COVID-19 outcomes.

Author contributions

All authors made equal contributions to the study design, statistical analysis, and drafting of the manuscript. The corresponding author, along with the co-authors, reviewed and approved the final version of the article prior to submission to this journal.

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Competing financial interests

The authors have no conflict of interest.

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